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# A Cation-Exchange Resin Artificial Kidney: Development and Metabolic Studies

By

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## INTRODUCTION

**A**CUTE renal failure may be precipitated by any of several etiologic factors. In the military patient, these causes are relatively few, and generally are related to either inadvertent transfusion of incompatible blood or the outcome of some severe form of injury. The latter may follow a surgical operation or be the result of massive trauma incurred during combat. The consequent renal insufficiency is often temporary in nature, and efforts are directed at prolongation of life by sustaining the patient through a critical phase of profound physiologic disturbances until secretion of urine is again resumed.

During World War II, it was not infrequent for individuals who suffered burial under debris or crushing-type injuries to develop anuria. Autopsy of such casualties during the bombardment of London disclosed that the renal dysfunction was due to necrosis of the renal tubules—that is, of the epithelial part of the nephron, whereas the glomeruli were intact.<sup>1</sup> Similar histologic changes appear to occur in many other instances of acute anuria, such as those accompanying shock or incompatible blood transfusions. It has become appreciated that the primary pathologic lesion in such states is a tubular one, and that acute anuria due to tubular necrosis is a reversible process, unless there is concomitant extensive glomerular disruption.<sup>2,3</sup> That treatment should be aimed toward obtaining a survival interval of approximately two weeks after the onset of anuria was recognized particularly in the Mediterranean Theater of Operations in

World War II and during the Korean conflict. Experiences in the care of casualties who developed post-traumatic renal insufficiency amply demonstrated that prolongation of life implied a greater incidence of diuresis and a higher over-all recovery record.<sup>4,5</sup> This goal was enhanced in Korea by the establishment of a renal insufficiency installation within helicopter range of the forward surgical hospitals.

The treatment of the patient with acute renal failure is mainly supportive. This involves, ideally, attempts at correction of the disturbed metabolic state by an expert team of physicians and nurses supplied with the proper equipment. Such optimal circumstances are rare in warfare, the Renal Insufficiency Center in Korea notwithstanding. An integral part of the treatment is the employment of extracorporeal dialysis by means of an artificial kidney. Even in the United States proper, institutions which possess artificial kidneys and personnel competent to operate them are limited to larger hospitals or medical centers, so that transportation of patients to these last-mentioned is almost mandatory. The situation which prevails in most combat zones is considerably more taxing. As expressed aptly by Teschan, "Some artificial kidneys may not inconceivably have to be dropped by parachute, may have to be flown 10,000 miles along with their supporting equipment, or be carried on men's backs over considerable distances. . . ."<sup>6</sup>

This paper will describe an artificial kidney based on the properties of ion-exchange resins. Preliminary investigations have revealed that the apparatus may be effective in prolonging survival during the early stages of acute renal shutdown, and that its compact structure and simple operation may make it well suited for use even in forward aid stations in combat areas.

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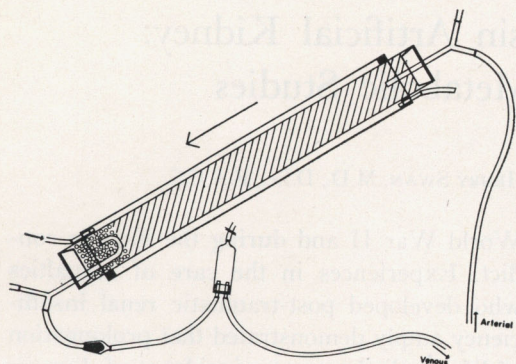


FIG. 1a. Apparatus of Muirhead and Reid. Subject's blood is circulated across an admixture of resins. Latter are regenerated periodically by flushing with a suitable solution via Y tubes. (*J. Lab. & Clin. Med.*, 33:841, 1948)

#### DEVELOPMENT OF ION-EXCHANGE RESIN ARTIFICIAL KIDNEY

*Historical.* The first published account of an artificial kidney was in 1913 by Abel, Rowntree and Turner.<sup>7</sup> They employed colloidion strips for dialysis, and ground the heads of leeches to obtain hirudin for anticoagulation. The procedure remained a laboratory curiosity until the momentous report in 1943 of Kolff and Berk, who demonstrated the feasibility of clinical hemodialysis by means of coiled cellophane tubing serving as a semi-permeable membrane of large surface area.<sup>8</sup> The patient's blood flows on one side of the membrane, and a suitable constituted rinsing fluid is placed on the opposite side to remove solutes which are transferred by virtue of a diffusion gradient. Numerous artificial kidneys patterned along the same principles have since been devised. The ones in most common use have the dimensions of a household washing machine, and necessitate the use of some 200 liters of prepared dialyzing solution. Hemodialysis is accomplished in from six to eight hours. It has been recently urged that this procedure be repeated daily for maximum prophylaxis in the treatment of acute renal failure.<sup>9</sup>

Following the suggestion of Elkinton and his associates,<sup>10</sup> cation-exchange resins have been employed either orally or by enema for the elimination of accumulated extracellular

potassium in renal failure. The enteric route is associated with sundry disadvantages, including nonpalatability, unpredictability of duration of response, occasional impaction of the mass, and sometimes acidosis. There have been endeavors to overcome these undesirable features by circulating the subject's blood directly across beds of ion-exchange resin.

The first "resin artificial kidney" was designed in 1948 by Muirhead and Reid.<sup>11</sup> The apparatus, shown in Figure 1a, consisted basically of a glass column, 85 cm. long and 4 cm. internal diameter, and contained 500 ml. of an admixture of cation- and anion-exchange resins. Sterility was attained by rinsing with ethanol. The resin bed was primed with blood, plasma or albumin. Hemoperfusion was conducted for 10 min. intervals, then interrupted, and the resin regen-

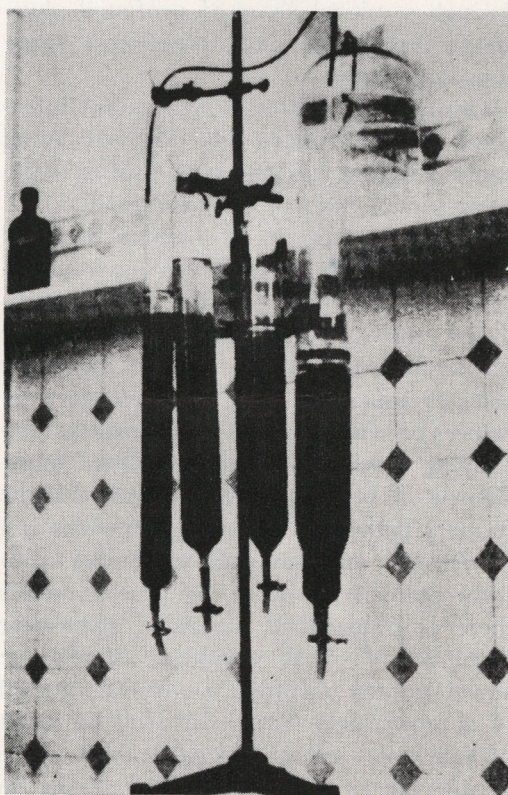


FIG. 1b. Apparatus of De Marchi and Bronniman. Blood is percolated through glass cylinders containing resin, then re-transfused. Wash solution is siphoned onto resin bed to regenerate it. (*Helvet. chir. acta*, 18:133, 1951)



erated with a suitable wash solution. The authors reported using this apparatus on six bilaterally-nephrectomized dogs, but only gave data for one animal in whom, after four such perfusions, a total of 3.5 Gms. of urea were extracted, and life prolonged by 2.5 days. No mention was made of potassium levels. Deacidite®, the granular anion-exchange resin employed, was noted to be partly soluble.

DeMarchi and Bronniman, in 1951, reported the use of resins for removing nitrogenous waste products from blood.<sup>12</sup> Their device, shown in Figure 1b, consisted of a series of glass columns half-filled with a cation-exchange resin. A given volume of blood was drawn from the subject, passed through a column, then re-transfused. This was performed a number of times, a fresh column being employed consecutively, and the preceding spent column reconstituted by washing. The resin was sterilized at the outset by suspension in concentrated acid. Pyrogenicity was mentioned as one of the drawbacks encountered. Results in reduction of hyperazotemia in a patient and a dog are reproduced in Figures 2a and 2b, respectively. Again, no data were provided on potassium concentrations.

In 1953, Kessler, Liebler, Abrahams and Sass described an ion-exchange resin artificial kidney for lowering elevated potassium levels in the blood.<sup>13</sup> Their apparatus was similar to that of Muirhead and Reid.<sup>11</sup> It consisted of a 125 ml. separatory funnel attached to a 30 cm. glass column which contained 180 Gm. of a cation-exchange resin. Sterility was accomplished by autoclaving. Hemoperfusion of eight uremic dogs was conducted for four to six hours in each case, and an average reduction of approximately 35 per cent obtained in extracellular potassium concentration after this flow period. The authors acknowledged the desirability of regenerating the resin, but stated that this would involve the frequent changing of columns, and make the procedure unwieldy.

The impractical characteristics of the aforementioned devices for clinical application are evident. Major problems are those

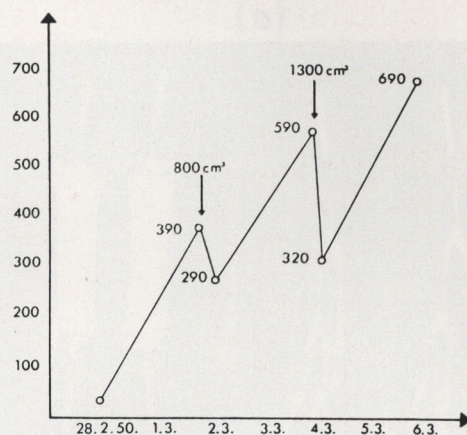
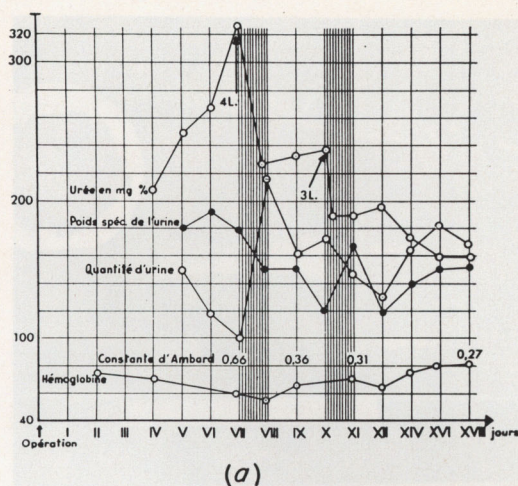


Fig. 2. Taux d'urée du chien néphrectomisé, en mg%.

FIG. 2. Reduction in urea effected with device of De Marchi and Bronniman. Arrows indicate volume of resin-treated blood in a patient (a) and dog (b) with uremia. (Helvet chir. acta, 18:133, 1951)

referable to sterility, freedom from pyrogenicity, absence of hemolysis or other deleterious intravascular side-effects, a means for effecting rapid replacement of active resin, and fool-proofing from external contamination. The mechanism of ion-exchange as a temporary substitute for the impaired kidney has remained an attractive challenge, however, and in 1955 Kolff himself stated that, "The future for the resin artificial kidney is practically unlimited and almost unexplored."<sup>14</sup>

*Authors' apparatus.* Thirty cation-exchange resins were screened in vitro for selective efficiency in the sequestration of po-



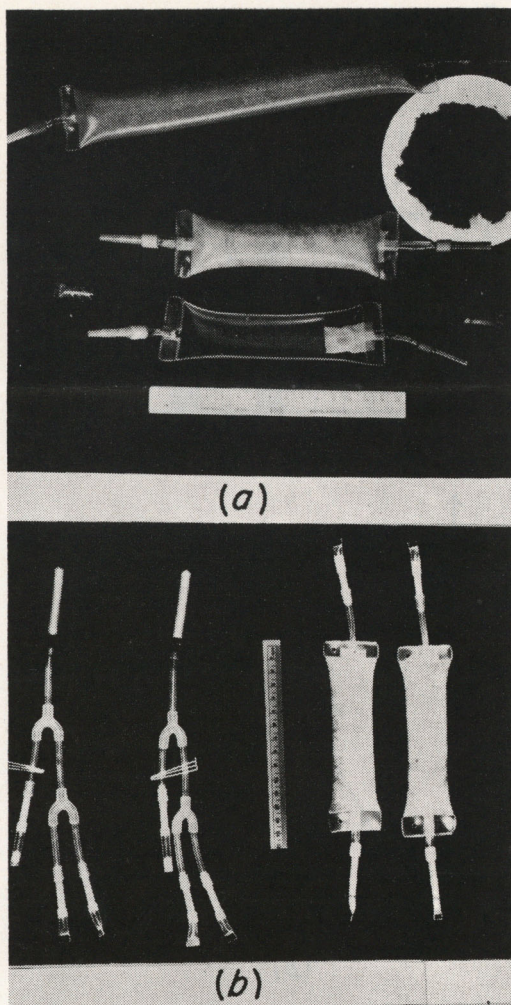


FIG. 3. Authors' apparatus. (a) Twenty-five and 50-Gm. columns shown. Right, amount of resin in 25-Gm. column. Below, longitudinal section through column. Inlet contains a stainless-steel ball-valve; outlet, a nylon filter of fine mesh size. (b) Sterile component parts included in sealed, waterproof envelope.

tassium from blood. Five of these proved to be satisfactory in their performance, and did not result in hemolysis upon contact of the blood with the resin particles. Further pilot investigations finally established a single resin, Dowex 50-X8, Na<sup>®</sup> (Dow Chemical Co., Midland, Mich.), as fulfilling all the requirements for safe hemoperfusion trial in the live subject. Dowex 50-X8, Na<sup>®</sup> is a synthetic sulfonated hydrocarbon polymer cation-exchange resin in the sodium cycle.

It is composed of non-hemolytic, insoluble, brown-colored beads of 50 mesh size.

The resin artificial kidney was manufactured commercially (Fenwal Laboratories, Somerville, N. J.), according to the authors' specifications. It is constructed in its entirety of vinylite, a hemorepellent polyvinyl plastic, and may be sterilized readily by autoclaving without damage to either the plastic container or its encased resin. As depicted in Figure 3a, each column is 12 cm. long, 2.8 cm. in diameter, has a wall 0.2 cm. thick, and contains 50 Gm. of resin supported on nylon bolting cloth filters of 100 mesh pore size. A stainless-steel ball-valve is present at the proximal orifice to obviate entrainment of resin spherules at the donor end. When the column is to be used the steel ball is pushed into the resin mass to permit unhindered blood flow. Columns 25 cm. in length and containing 100 Gm. of resin are also available. Figure 3b shows the main components of the apparatus from the waterproof envelope in which they are packed. Other sealed, pocket-size packs contain a supply of sterile resin columns.

Figures 4a and 4b reveal two varieties of the assembled apparatus. There are two resin columns, in parallel, which can be attached or dismantled easily by means of connectors. The inflow (influent) limb consists of a sheathed 15-gauge laminar flow needle fastened to a Y-connector, one arm of which may be employed for sampling of the blood before percolation through the resin mass. The other arm leads to another Y-connector equipped with adapters to which the resin columns are joined. The outflow (effluent) system is similar to the inflow limb in one model. In the other model, a plastic container of known capacity which is inserted in tandem at the outflow end enables relatively accurate determination of blood flow through the apparatus, and also permits pressure transfusion of the resin-treated blood, if desired.

The needle of the inflow tube is introduced into an artery, and blood allowed to fill the entire apparatus. Less than 30 ml. of blood are required, so that priming with bank



blood is unnecessary. The effluent limb needle is then inserted into a vein, and hemoperfusion started. Fresh resin columns are substituted at selected time intervals. In order to maintain an uninterrupted stream of blood in the circuit, replacement of the columns is performed alternately as follows: Clamps are applied immediately proximal and distal to a column. The latter is disconnected and discarded. A fresh column is attached to the proximal adapter and allowed to fill with blood, following which it is connected to the distal adapter and the adjoining clamp removed to enable blood to circulate.

Less than 10 ml. of blood are lost with each discarded column.

A pump is not employed. Because of the small dimensions of the apparatus and the minimal resistance opposed to flow, the subject's blood pressure is sufficient for unhindered circulation.

#### METABOLIC STUDIES

*Method.* Twenty adult mongrel dogs were subjected to one-stage bilateral nephrectomy. After recovering from the operation, five were observed untreated, while the other 15 were treated with the resin artificial kidney.

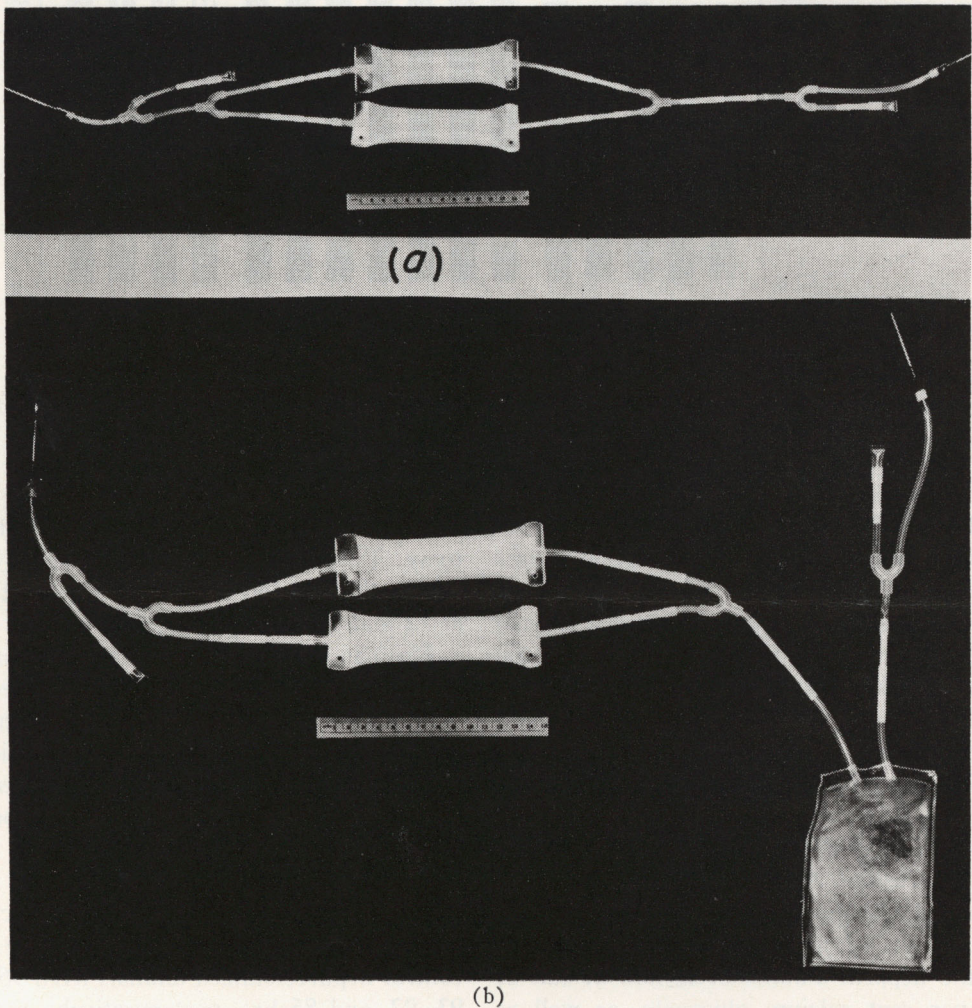


FIG. 4. Two models of ion-exchange resin artificial kidney. Influent limb at left. Laminar-flow needles are fused to tubing. In (b), plastic container of known volume is incorporated in effluent limb, and may be used for determination of blood flow, or for pressure transfusion.



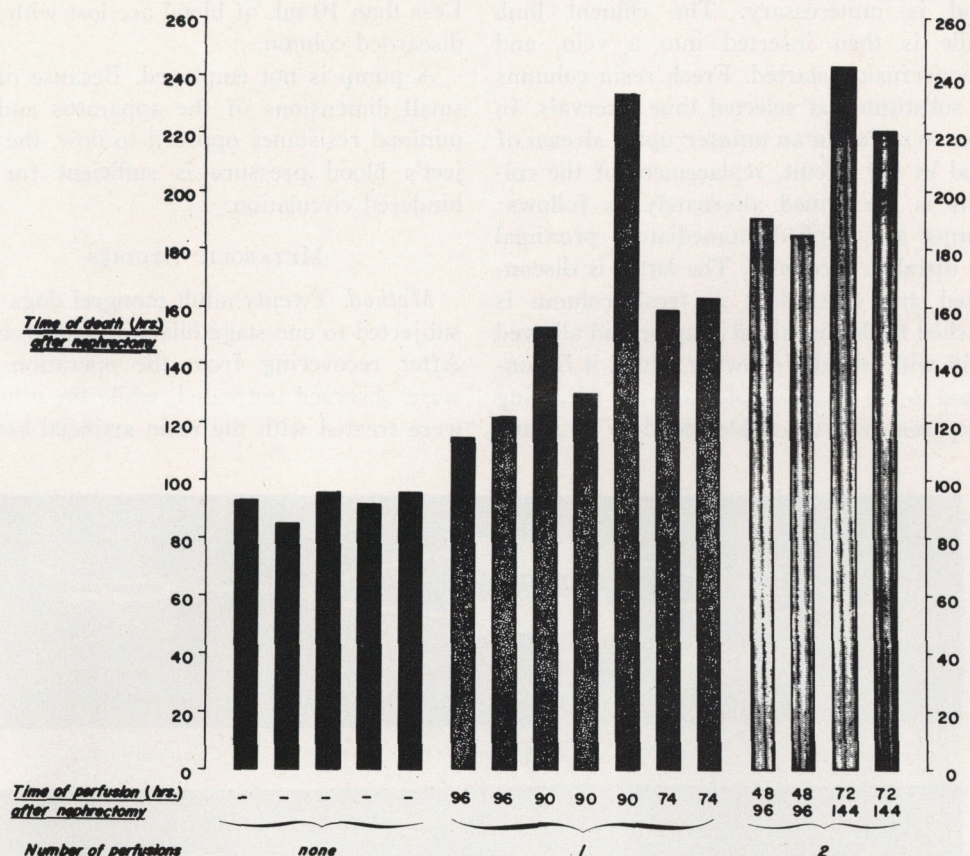


Fig. 5. Effect of hemoperfusion on survival time of bilaterally nephrectomized dogs. Repeated perfusion appears to result in net prolongation of survival.

In the latter group, anesthesia was induced and maintained with minimal doses of intravenous sodium pentothal. Two hundred units of sodium heparin per Kg. body weight were administered. The blood flow was from femoral artery to the contralateral femoral vein. Fresh resin columns were substituted every 15 mins. on an empiric basis. Hemoperfusion was conducted for at least 60 mins. Blood samples were withdrawn from the influent side-arm initially, at 15 min. intervals during perfusion, and 30 mins. following perfusion. After the last sample was obtained, the animal was given intravenously an amount of protamine sulfate equivalent to the heparin administered, and 20 ml. of 10 per cent calcium gluconate, as well as 500 mg. of oxytetracycline intramuscularly.

The treated animals were divided into a group subjected to only one hemoperfusion and another series subjected to two spaced

hemoperfusions. Eleven of the treated group were perfused at 74 to 96 hrs. after nephrectomy. Two of the remaining animals were perfused at 48 and 96 hrs., and the last two at 72 and 144 hrs. post-nephrectomy.

Plasma sodium and potassium concentrations in the samples were determined by internal flame photometry. Blood urea nitrogen was measured by direct nesslerization.<sup>15</sup> Serum calcium was determined by a spectrophotometric technic using sodium chloranilate,<sup>16</sup> and magnesium levels by the titan yellow method.<sup>17</sup>

**Results.** Figure 5 shows the effect of hemoperfusion on survival time. The five control nephrectomized animals lived 96, 96, 93, 92, and 85 hrs. postoperatively, that is, 92.4 hrs. on the average. Seven of the animals in the group perfused once were observed until their demise. Death occurred within a range of 115 to 234 hrs. after



nephrectomy, the average being 153.7 hrs. The other four dogs in the group were sacrificed three hours after perfusion. There was no gross evidence of bleeding from, or injury to, any organs of the body. Of the animals perfused twice, those treated at 48 and 96 hrs. lived 191 and 185 hrs. postoperatively. The two animals treated at 72 and 144 hrs. lived for 243 and 221 hrs. following nephrectomy. The average survival period for these four dogs was 210 hrs. Thus, repetition of the procedure resulted in a net

increase in the survival span.

Figure 6 shows urea nitrogen to have been affected only slightly, the blood norm never being attained. The pre-treatment mean level of 202.9 mg. per 100 ml. dropped to 175.8 mg. per 100 ml. at 60 mins., and rose to 177.2 mg. per 100 ml. 30 mins. after treatment.

Figures 7 and 8 reveal the influence of hemoperfusion on the arithmetic mean levels of blood cations. Prior to perfusion, the average potassium concentration was 8.0

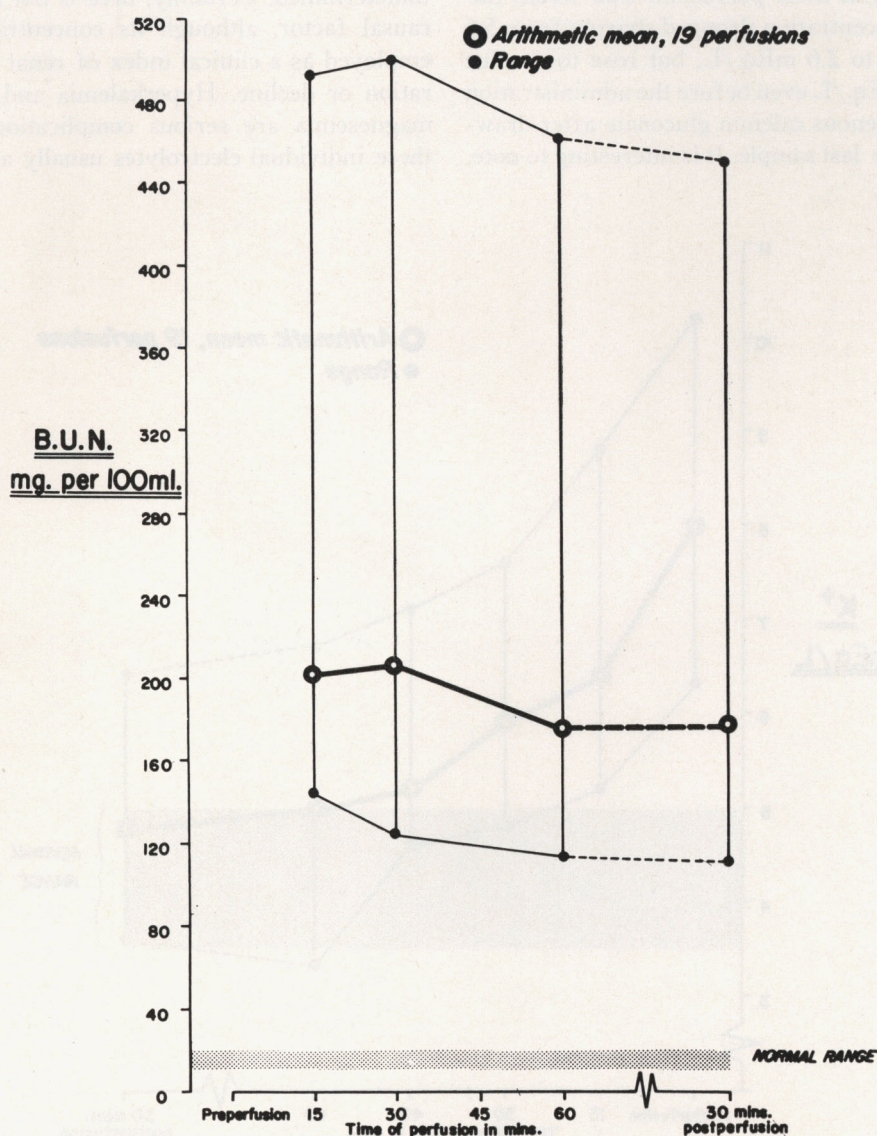


FIG. 6. Effect of perfusion on blood urea concentration in bilaterally nephrectomized dogs. There is a decrease, but this is slight, and the blood norm is not attained.



mEq./L. After perfusion for 60 mins., the potassium concentration was 5.0 mEq./L, and 30 mins. after cessation of perfusion it was 4.8 mEq./L. The mean sodium level rose slightly during perfusion, increasing from an initial value of 138.4 mEq./L to 145.5 mEq./L at the conclusion of perfusion. The latter increment resulted in a level still within the normal blood range, and represents ionic replacement since the resin employed is in the sodium cycle. The serum magnesium level declined from the original 3.1 mEq./L to 1.7 mEq./L at the end of perfusion, and 1.6 mEq./L after perfusion. The serum calcium concentration dropped sharply from 5.6 mEq./L to 2.6 mEq./L, but rose to a value of 3.1 mEq./L even before the administration of intravenous calcium gluconate after drawing of the last sample. It is interesting to note,

moreover, that none of the treated animals developed tetanic manifestations or bleeding at any time during the procedure, despite the subnormal calcium concentration.

#### COMMENTS

In the uremic syndrome, patients with prolonged renal insufficiency become critically ill because of the accumulation of metabolic substances ordinarily excreted by the normal kidney. The precise identities of all the retention products responsible for this complex syndrome are as yet undetermined. Certainly, urea is not a prime causal factor, although its concentration is employed as a clinical index of renal amelioration or decline. Hyperkalemia and hypermagnesemia are serious complications, and these individual electrolytes usually accumu-

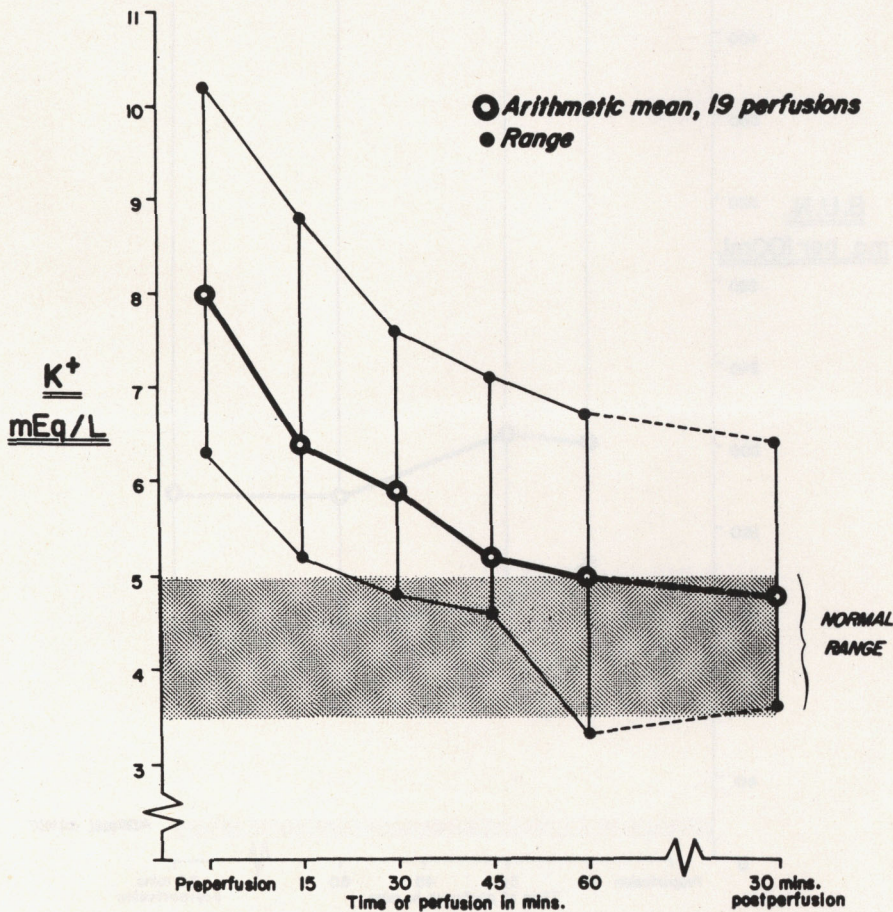


FIG. 7. Effect of perfusion on extracellular potassium level in bilaterally nephrectomized dogs, revealing a substantial decline.



late quite rapidly even in the early phases of renal shutdown. Potassium intoxication is particularly lethal since it is a not infrequent cause of death. Calcium concentrations decrease in the blood in renal failure, but replacement of this mineral ion is ordinarily

achieved without undue difficulty by intravenous infusion.

The apparatus which has been described in this paper appears to fulfill effectively the immediate need for reducing hyperkalemia and hypermagnesemia in a comparatively

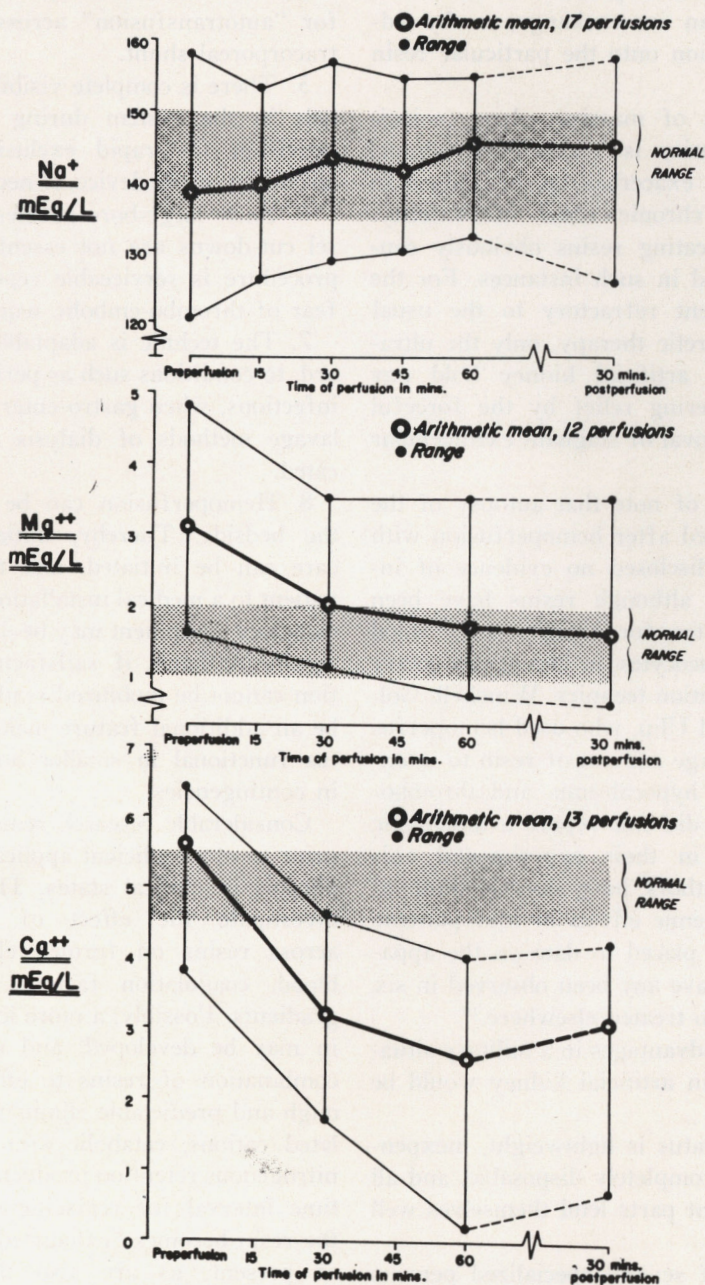


FIG. 8. Effect of perfusion on level of other blood cations in bilaterally nephrectomized dogs. The serum sodium concentration remains in the normal range. Magnesium undergoes a significant decrease. Calcium drops sharply, but the level shows a return even before infusion of calcium gluconate.



short period of time. There is possibility of similarly accomplishing a reduction of urea and other nitrogenous products by incorporation into the device of a suitably prepared resin. Since urea is not an electrolyte, a satisfactory resin would need to function by the physico-chemical process of ion-exclusion rather than ion-exchange, or by adsorptive attraction onto the particular resin moiety.

The problem of massive edema, coincident with anuria, is encountered almost solely in acute exacerbations of failure in patients with chronic renal insufficiency. Sodium-reciprocating resins obviously cannot be employed in such instances. For the occasional patient refractory to the usual methods of diuretic therapy, only the ultra-filter types of artificial kidney hold any promise of offering relief by the forceful mechanical removal of stagnant extracellular fluid.

It is worthy of note that autopsy of the animals sacrificed after hemoperfusion with the apparatus disclosed no evidence of internal bleeding although resins have been employed *in vitro* for extraction of blood platelets and leucocytes, in lieu of customary precipitation-elution technics. Winchell, Golub, Ehrlich and Ulin, who used hemoperfusion across a large amount of resin to intentionally induce hypocalcemia and thrombocytopenia, also did not report hemorrhagic manifestations in their experimental animals.<sup>18</sup> The authors have not encountered any injurious hemic effects in four patients who have been placed to date on the apparatus, neither have any been observed in six other patients so treated elsewhere.<sup>19</sup>

The diverse advantages in a military situation of the resin artificial kidney would be manifold:

1. The apparatus is lightweight, inexpensive, compact, completely disposable, and all of its constituent parts lend themselves well to autoclaving.

2. A team of several specialized persons is not required to perform hemoperfusion.

3. Large volumes of rising fluids are unnecessary, and priming with blood or plasma dispensed with. This enhances con-

trol of relative constancy in blood volume, and ensures freedom from exogenously-elicited disturbances in hydrostatic pressure.

4. While a pump might expedite perfusion, neither it nor other noisy electrical appliances are needed if the patient is not in shock, and his blood pressure is adequate for "autotransfusion" across the small extracorporeal shunt.

5. There is complete visibility of all channels in the system during operation, and provision for rapid exclusion and short-circuiting of the device, if necessary.

6. Since large-bore needles are used, vessel cut-downs are not essential, so that the procedure is serviceable repeatedly without fear of thrombo-embolic sequelae.

7. The technic is adaptable, without hazard, to conditions such as peritonitis or other infections, when gastro-enteric or peritoneal lavage methods of dialysis are contraindicated.

8. Hemoperfusion can be carried out at the bedside. Thereby, initial and prompt care can be initiated, and transfer of the patient to a medical installation housing more elaborate equipment may be deferred without significant harm if satisfactory transportation cannot be mobilized readily. This would be an additional feature making the apparatus functional in smaller hospitals for use in contingencies.

Considerable research remains to be done prior to more efficient application of the apparatus in clinical states. There is need to investigate the effect of hemoperfusion across resins on formed elements of the blood, coagulation factors and osmolality gradients. Possibly, a more ion-selective resin may be developed, and use made of a combination of resins to effect more thorough and predictable elimination of accumulated cations, catabolic aromatic acids and nitrogenous retention products. The optimum time interval for replacing columns before the resin becomes "exhausted" is speculative at present, as are also the number of perfusions and spacing between the latter after the onset of anuria to extend survival. Longer columns may be more appropriate for humans than the present arrangement;



but this would doubtlessly necessitate the interposition of a pump in the system to overcome such mechanical factors as resistance, turbulence, eddying and channeling of blood through the resultant greater resin mass. Such a modification, admittedly a warranted refinement, might serve to diminish the perfusion time and number of column changes, but would also, in effect, probably encumber an otherwise uncomplicated device.

## SUMMARY

1. A simple, inexpensive and compact extracorporeal device for use in the management of acute renal failure has been described.

2. The apparatus is completely disposable and easily sterilized. It consists, essentially, of columns of an insoluble and non-hemolytic cation-exchange resin across which hemoperfusion is performed.

3. Dogs rendered anuric by bilateral nephrectomy were treated with this apparatus. The survival time was prolonged significantly. There was substantial diminution in the concentrations of extracellular potassium, calcium and magnesium. The serum calcium level was restored in part by intravenous infusion of the gluconate salt. The blood urea nitrogen was decreased but slightly. The serum sodium level was augmented, but this increase did not extend beyond the limits of normal.

4. No tetanic or hemorrhagic manifestations were discerned during performance of the procedure.

5. The apparatus may prove valuable in military situations as an adjunct in the early care of patients with hyperkalemia and hypomagnesemia until they can be transported to specializing centers having more elaborate equipment and trained personnel.

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